

Advances in the Surgical and Ablative Management of Colorectal Liver Metastases

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Abstract. Introduction. Colorectal liver metastases (CRLM) represent a critical challenge in the management of colorectal cancer (CRC), occurring in approximately 25% of patients. The liver is the most common site for metastatic spread, significantly impacting prognosis and treatment options. **Aim.** This study aims to review the current understanding of CRLM management, focusing on epidemiology, surveillance, surgical and ablative techniques, and the role of multidisciplinary teams in optimizing patient outcomes. **Method:** A comprehensive literature review search across multiple databases such as PubMed and Clarivate was conducted, synthesizing data on the epidemiology of CRLM, surveillance strategies, surgical approaches, and ablative therapies. **Results.** The management of colorectal liver metastases (CRLM) has developed into a comprehensive and multifaceted approach. Early detection via routine imaging and biomarker analysis is paramount. Surgical options, including R0 resection and two-stage hepatectomy, combined with ablative techniques such as radiofrequency and microwave ablation, have demonstrated significant improvements in survival rates. Moreover, advancements in systemic therapies have expanded the window for resection in previously unresectable cases, significantly improving survival outcomes. **Conclusions.** The intricate nature of liver metastasis in colorectal cancer requires an integrated treatment strategy that encompasses surgical, ablative, and systemic therapies. Continuous research into biomarkers and innovative treatment methods will further refine personalized interventions, enhancing survival and quality of life for patients with CRLM. The collaboration of multidisciplinary teams is crucial for delivering optimal care and improving treatment outcomes.

Key words: major hepatic surgery, colorectal metastasis, management

Introduction

Colorectal cancer (CRC) ranks among the most prevalent cancers globally, being the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality. However, in recent decades, survival rates for CRC patients have markedly improved, particularly for those

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with metastatic disease. In the 1990s, the two-year overall survival (OS) rate for stage IV CRC was a mere 21% (1). However, this pattern has risen to an impressive 35-40% five-year OS in the 2010s (2) and 67% in 2019 (3). This advancement can be largely attributed to enhancements in systemic chemotherapy, surgical techniques, and perioperative care, which have collectively increased the number of patients eligible for surgical intervention for metastatic CRC.

Liver metastasis represents a significant clinical challenge, particularly in patients with colorectal cancer, where it is the most prevalent site of metastatic disease. Approximately 15-25% of patients presenting with metastatic disease at initial diagnosis, while an additional 18-25% will develop distant metastases within five years. (4), (5)

A multidisciplinary approach to managing metastatic CRC has been crucial in improving OS, transitioning from a focus on palliative care to more aggressive treatment strategies. Careful evaluation by a multidisciplinary team is essential, as treatment choices and sequencing vary based on tumor presentation, the number and location of metastases, and the feasibility of surgical resection.

Diagnostic Criteria for Liver Metastasis

The diagnosis of liver metastasis requires a multifaceted approach, incorporating clinical evaluation, advanced imaging modalities, laboratory analyses, and, in select cases, histopathological confirmation. This comprehensive assessment is essential for accurate diagnosis and subsequent therapeutic planning.

Ultrasound serves as an initial imaging modality due to its accessibility and non-invasive nature. It is effective in detecting liver lesions and assessing hepatic morphology. Depending on the

characteristics of the primary tumor, metastatic lesions may present as hypoechoic or hyperechoic areas. Despite its utility, ultrasound may be limited in its ability to detect small or deeply situated lesions, necessitating further imaging in many cases. (6)

Computed tomography (CT), particularly contrast-enhanced CT, is widely regarded as the gold standard (7) for the detection of liver metastases. This imaging modality provides high-resolution anatomical detail, allowing for precise differentiation between benign and malignant hepatic lesions. Typical radiological findings of liver metastases on contrast-enhanced CT include well-defined hypoattenuating lesions during the portal venous phase, with varying degrees of contrast enhancement depending on the origin and characteristics of the primary tumor. (8)

Magnetic resonance imaging (MRI) has emerged as a valuable tool, particularly in cases where CT findings are inconclusive or further characterization of lesions is required. MRI sequences, such as diffusion-weighted imaging (DWI), enhance the sensitivity for detecting metastatic liver lesions, particularly in patients with colorectal cancer. (9) MRI also offers superior soft tissue contrast, which aids in the detailed visualization of liver metastases and the assessment of surrounding hepatic parenchyma. (10)

In addition to imaging modalities, tumor biomarkers, particularly carcinoembryonic antigen (CEA), play a critical role in the diagnosis and monitoring of colorectal liver metastases. Elevated CEA levels may indicate metastatic progression and can be used to assess treatment response and disease recurrence. (11)

The integration of these diagnostic tools is crucial for the classification of liver metastases into resectable (Class I and II) or

unresectable categories. This classification is performed during multidisciplinary team meetings and is essential for guiding therapeutic decisions, including the feasibility of surgical resection and the selection of chemotherapy protocols.

Resectability of Metastases

The evaluation of liver metastasis resectability is a critical decision guided by a multidisciplinary team (MDT) with expertise in hepatobiliary surgery. Around 70% of liver metastases are initially deemed unresectable. The classification of resectability into Class I, Class II, or unresectable informs the therapeutic approach and the associated chemotherapy regimen. (12,13)

Class I metastases, which are resectable at the time of diagnosis, are typically managed with perioperative chemotherapy, most commonly the FOLFOX regimen, administered over a six-month period—three months pre-operatively and three months post-operatively. (14) In contrast, Class II metastases, which may require more complex surgical interventions or conversion to resectable status following induction therapy, are initially treated with a combination of chemotherapy and targeted agents. These regimens include a chemotherapy doublet with anti-EGFR antibodies for RAS/BRAF wild-type tumors, or a triplet with bevacizumab. (15,16) In cases where liver resection is technically challenging, a staged approach may be employed, beginning with tumor resection, followed by portal vein embolization to promote liver hypertrophy, and concluding with hepatectomy. Following surgery, additional cycles of FOLFOX chemotherapy are typically administered, assuming the absence of residual neuropathy, with a goal of completing 12 total treatment cycles.

For patients with initially unresectable liver metastases, regular

reassessments by the MDT are essential to identify opportunities for alternative therapies. These may include local ablative interventions, such as microwave or radiofrequency ablation, cryotherapy, or stereotactic irradiation, or to assess whether systemic therapy has sufficiently reduced the tumor burden to allow surgical resection. (17,18) Some factors, such as the involvement of both portal pedicles or multiple suprahepatic veins, are absolute contraindications to surgery. However, relative contraindications—such as the presence of large (>5 cm), numerous (>3), or bilobar metastases, elevated CEA levels, or regional lymph node involvement—while increasing the risk of recurrence, do not completely rule out surgical options. (19)

Recent studies have examined the potential benefit of hepatic intra-arterial chemotherapy (HIAC) following resection of liver metastases. Although preliminary results are mixed, trials such as PRODIGE-43/PACHA-01 (20) suggest that HIAC may prolong liver-recurrence-free survival. This approach is being considered for selected patients in specialized centers and is frequently discussed in MDT evaluations.

Surgical Techniques for Colorectal Liver Metastases (CRLM)

Surgical resection remains the cornerstone of potentially curative treatment for colorectal liver metastases (CRLM) (21). The complexity of the surgical approach is dictated by several factors, including the number, size, and location of metastases, the patient's overall health, and the liver's functional capacity. Below is an overview of the key surgical strategies employed in managing CRLM. Figure 1. (22)

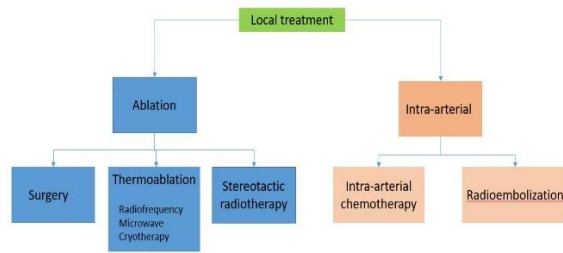


Figure 1. Local treatment of CRLM (after Cervantes A et al., Ann Oncol. 2023)

A. Resection of R0-Resectable Colorectal Liver Metastases

R0 resection refers to the complete removal of all visible tumors, ensuring that no cancer cells remain at the margins of the resected tissue. This technique is associated with the most favorable long-term survival outcomes, with five-year survival rates reported between 20% and 45%. (23)

Criteria for determining R0 resectability involve both technical and oncological factors. From a technical standpoint, tumors must be removable while leaving at least 30% of functional liver tissue intact. Resection is feasible regardless of the number or size of metastases or bilobar involvement, as long as sufficient liver volume remains post-operatively.

Oncological factors also play a critical role in determining the surgical approach. The timing of metastasis onset (whether synchronous or metachronous), the biological behavior of the tumor, and the presence of extrahepatic disease are important considerations. Additionally, molecular markers such as RAS and BRAF mutation status, as well as microsatellite instability (MSI), influence surgical decision-making and prognosis. (17,18)

B. Parenchyma-Sparing Techniques in Liver Surgery

In cases of CRLM, parenchyma-sparing techniques are employed to maximize the preservation of healthy liver tissue. This approach is especially important

for maintaining postoperative liver function and minimizing complications associated with extensive liver resections. (24) (25)

Parenchyma-sparing surgery includes anatomical resections, where only the tumor-bearing segments of the liver are removed, allowing for the maximum retention of healthy liver tissue. This strategy is particularly effective for patients with solitary or limited metastases, ensuring that functional liver capacity is preserved while achieving oncological safety.

C. Techniques and Rationale

Surgical resection is the only potentially curative treatment for colorectal liver metastases (CRLM). The choice of surgical approach depends on several factors, including the size, number, and location of metastases, as well as the patient's overall health and liver function. Below is a detailed overview of key surgical techniques for managing CRLM (26)

1. Anatomical Resection

Anatomical resection involves removing specific liver segments along with the tumor, aiming to preserve as much healthy liver tissue as possible. This technique is particularly effective in patients with solitary or limited metastases, where precise removal can be achieved without compromising liver function. It minimizes the sacrifice of functional liver parenchyma while ensuring the complete resection of tumor tissue. (27)

2. Two-Stage Hepatectomy (TSH)

For patients with bilobar metastases or when a large portion of the liver is affected, a single-stage resection may not be feasible. Two-stage hepatectomy (TSH) is employed in these cases. In the first stage, tumors in one lobe of the liver are resected, while techniques such as portal vein embolization are used to promote hypertrophy of the remaining liver. In the

second stage, once the non-tumorous liver has sufficiently grown, the remaining metastases are resected. This technique ensures adequate liver regeneration between surgeries and reduces the risk of liver failure. (28) (29) (30)

3. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

The ALPPS technique is designed for patients who require rapid liver regeneration before resection, particularly when insufficient liver remnant volume would otherwise preclude surgery. The liver is surgically divided, and the portal vein is ligated to reduce blood flow to the tumor-bearing section. This accelerates hypertrophy of the future liver remnant, allowing the second-stage resection to occur sooner than with traditional two-stage hepatectomy. ALPPS, however, carries higher morbidity risks and should be performed in specialized centers with expertise in complex liver surgeries. (31, 32)

4. Portal Vein Embolization (PVE)

Portal vein embolization (PVE) is a pre-surgical strategy used to increase the volume of the future liver remnant (FLR) in patients with insufficient liver reserve. In this technique, the portal vein supplying blood to the tumor-bearing liver is blocked, which stimulates growth in the healthy part of the liver. Once sufficient liver hypertrophy is achieved, the resection of the diseased portion can be safely performed. PVE enhances the safety of resections in patients with initially inadequate liver volumes. (33)

5. Robotic, Laparoscopic and Open Liver Resection

Liver resections can be performed using either laparoscopic or open approaches.

Robotic liver resection (RLR) is considered a safe and feasible option for patients with colorectal liver metastases (CRLM). The experts recommend robotic

liver resection (RLR) as a safe and feasible option for patients with colorectal liver metastases (CRLM), as it is associated with a lower conversion rate but a longer hospital stay compared to laparoscopic liver resection (LLR). (33) Although the evidence is limited, it indicates no significant differences in perioperative outcomes between RLR and open liver resection (OLR). Similarly, the available oncologic data suggest no substantial differences between RLR and both LLR and OLR. However, the level of evidence supporting these conclusions is very low, and the strength of the recommendation remains weak (Grade 2D), with 89.66% expert agreement. (34)

Laparoscopic liver resection is a minimally invasive technique suitable for smaller, superficial, or technically easier-to-resect metastases. It offers advantages such as reduced recovery time, less postoperative pain, and shorter hospital stays. However, it requires advanced surgical expertise and may not be appropriate for larger, deeper, or more complex tumors. (35)

Open liver resection remains the traditional approach for larger, multiple, or bilobar metastases requiring extensive resection. This method allows for better visualization and access during complex procedures, such as major hepatectomies or combined colorectal surgeries. (36)

6. Synchronous Resection of Primary Colorectal Tumor and Liver Metastases

In select patients, it is possible to perform synchronous resection, where both the primary colorectal tumor and the liver metastases are removed during the same operation. This approach reduces overall treatment time and hospital stays. It is particularly suitable for patients with a limited disease burden and good overall health. However, the complexity of the surgery increases operative risk, especially

for patients with extensive liver involvement. (37) (38)

7. Combination of Resection and Ablation

For patients in whom complete surgical resection is not feasible due to the location or number of metastases, a combination of resection and ablative techniques can be employed. Resectable tumors are surgically removed, while smaller, less accessible, or unresectable lesions are treated with ablative methods such as radiofrequency or microwave ablation. This combined approach maximizes the chances of clearing all cancerous tissue, particularly in cases of bilobar disease, while preserving liver function. (39)

8. Liver Transplantation (Experimental)

Historically, liver transplantation was considered too high-risk for patients with metastatic colorectal cancer. However, recent advances have led to renewed interest in this approach for selected cases. Liver transplantation is currently reserved for clinical trials or highly select patients with stable and well-controlled metastatic disease. It is being investigated as a potentially curative option in cases where liver resection is not feasible due to extensive metastases. (40)

D. 3D Simulation in Liver Surgery for CRLM

The application of 3D simulation technology in liver surgery has garnered increasing attention, particularly in the preoperative planning of complex cases involving bilobar colorectal liver metastases (CLMs). This is especially relevant for predicting future liver remnant (FLR) in procedures like R1 vascularized one-step hepatectomy (R1vasc-OSH), where precise FLR estimation is critical for achieving

successful surgical outcomes and minimizing postoperative complications.

While the traditional hand-tracing technique continues to be the gold standard for liver volume assessment, 3D simulation offers a more standardized and efficient method for FLR estimation. This technology reduces reliance on manual processes and enhances the accuracy of preoperative planning. (33) Although some minor discrepancies were observed between predicted and actual FLR, particularly in patients with high tumor burden, 3D simulation has proven to be highly reliable in estimating liver volumes.

Clinical outcomes from the use of 3D simulation indicate improved surgical performance, with no reported mortality in patients undergoing R1vasc-OSH, compared to a higher rate of postoperative liver failure in those treated without 3D simulation. These findings suggest that the use of 3D simulation enhances patient selection and surgical planning, making complex parenchyma-sparing surgeries more feasible. (41)

Despite the advantages, challenges remain regarding the technical demands of 3D simulation, as well as the need for further external validation of results. Nevertheless, 3D analysis provides a reliable and valuable tool for FLR estimation, contributing to safer and more effective surgical interventions in liver resection cases.

Ablation Techniques for CRLM

Ablation techniques are essential options in the management of colorectal liver metastases (CRLM), particularly for patients who are not candidates for surgical resection due to the location, size, or number of lesions. These minimally invasive procedures aim to destroy tumor cells while preserving surrounding healthy liver tissue, thereby maximizing the chance of long-term survival.

Here are the primary ablation techniques used in clinical practice:

Ablation techniques are integral to the management of colorectal liver metastases (CRLM), particularly for patients who are unsuitable for surgical resection due to the size, location, or number of lesions. These minimally invasive procedures aim to eradicate tumor cells while preserving surrounding healthy liver tissue, thus enhancing the prospects for long-term survival. Below are the primary ablation techniques used in clinical practice:

1. Radiofrequency Ablation (RFA)

RFA employs high-frequency radio waves to generate heat that effectively destroys cancer cells. The procedure involves inserting a needle-like electrode into the tumor, guided by imaging modalities such as ultrasound or CT. (42, 43) This technique is generally indicated for small tumors (≤ 3 cm) and is particularly effective for unilobar metastases. As a minimally invasive option, RFA can be performed percutaneously or laparoscopically, resulting in shorter recovery times and reduced hospitalization. Studies indicate local control rates of 80-90% for small tumors, with five-year survival rates comparable to surgical resection in select patients.

2. Microwave Ablation (MWA)

MWA, like RFA, uses heat to ablate tumors but operates at microwave frequencies, allowing for the treatment of larger tissue volumes more efficiently. (44) This technique is suitable for larger tumors and may be more effective than RFA in cases where the tumor size or proximity to major blood vessels limits the efficacy of radiofrequency waves. MWA's faster ablation speed and larger zones of treatment make it a valuable alternative, particularly for tumors ≤ 5 cm. Clinical studies suggest that MWA provides effective local control and

comparable survival outcomes to RFA, especially for larger tumors. (45)

3. Cryoablation

Cryoablation utilizes extreme cold to freeze and destroy tumor cells. A probe is inserted into the tumor, and freezing temperatures are achieved using circulating liquid nitrogen or argon gas. (46) Cryoablation is typically reserved for lesions that are challenging to access or where other ablation methods may present a risk to nearby structures. This technique may offer advantages for tumors located near critical structures, as it creates a "safety margin" of frozen tissue around the lesion. (47) Although cryoablation is less commonly used than RFA or MWA, it can still achieve favorable local control rates.

4. Stereotactic Body Radiation Therapy (SBRT)

SBRT delivers highly precise, targeted radiation doses directly to the tumor, minimizing damage to surrounding healthy tissue. It typically requires a few high-dose treatments rather than the conventional fractionated radiation approach. (48,49) SBRT is particularly suitable for patients with limited metastatic disease who are not candidates for surgery or thermal ablation. The technique is effective for treating tumors that are otherwise difficult to access and may be beneficial for patients with multiple metastases. (50)

5. Selective Internal Radiation Therapy (SIRT)

SIRT involves the direct injection of radioactive microspheres into the hepatic artery, which feeds the tumor, thereby delivering localized radiation. This technique maximizes the radiation dose to the tumor while minimizing exposure to healthy liver tissue. (51) SIRT is generally indicated for patients with unresectable or oligometastatic disease and can be considered when other ablation techniques are unsuitable. It can treat

larger tumors and multiple lesions simultaneously and may offer survival benefits in select populations. Preliminary data suggest that SIRT can extend survival and improve quality of life in patients with advanced liver metastases. (52)

Prediction Score for 10-Year Survival in Colorectal Liver Metastases (CRLM)

Accurately predicting long-term outcomes for patients with colorectal liver metastases (CRLM) undergoing resection is critical for guiding treatment strategies and patient management. The development of a comprehensive 10-year survival prediction model integrates 15 independent factors that capture the complexity of tumor biology, patient characteristics, and therapeutic interventions. These factors are used to create a prognostic score that stratifies patients based on their likelihood of long-term survival, facilitating personalized treatment plans. (53, 54)

The 15 predictive factors include:

1. Age: Older patients generally have a lower survival rate, influencing treatment aggressiveness.
2. Gender: Some studies suggest that gender may influence response to treatment and survival outcomes.
3. Primary Tumor Location: Tumors originating in the rectum may behave differently than those in the colon, affecting prognosis.
4. Nodal Status of the Primary Tumor: Positive nodal status indicates a higher tumor burden, reducing survival odds.
5. Disease-Free Interval: A longer interval between treatment of the primary tumor and the detection of metastases is associated with better outcomes.
6. Number of Liver Metastases: The number of metastases significantly impacts resectability and long-term survival.
7. Diameter of the Largest Metastasis: Larger metastases are associated with poorer

outcomes, as they are more likely to be aggressive or advanced.

8. Preoperative CEA Levels: Elevated carcinoembryonic antigen (CEA) levels are linked to a higher risk of recurrence and worse survival.

9. Resection Margin Status: Positive margins (R1) after resection suggest residual disease, leading to a higher chance of recurrence.

10. Presence of Extrahepatic Disease: The existence of metastases outside the liver is a poor prognostic indicator, often contraindicating surgery.

11. KRAS Mutation Status: The presence of KRAS mutations is associated with poorer survival due to more aggressive tumor biology.

12. BRAF Mutation Status: BRAF mutations, though less common, predict an even worse prognosis than KRAS mutations.

13. Histopathological Growth Patterns: Certain growth patterns of liver metastases correlate with a higher likelihood of recurrence.

14. Perioperative Systemic Chemotherapy: The use of chemotherapy before or after surgery can influence survival, improving outcomes in responsive tumors.

15. Hepatic Arterial Infusion Pump (HAIP) Chemotherapy: This targeted chemotherapy delivered directly to the liver may enhance local control of metastatic disease.

These factors are combined into a predictive score, which helps categorize patients into different risk groups, ranging from those with a favorable prognosis to those with a high likelihood of poor outcomes. This scoring system serves as a valuable tool in clinical decision-making, allowing for personalized treatment plans and more accurate discussions of prognosis with patients. The stratification of patients based on these factors also enables better selection

for surgical interventions, ensuring that high-risk patients are managed more conservatively or with additional systemic therapies.

Conclusion

Liver metastasis remains a major challenge in the management of colorectal cancer (CRC), with approximately 25% of patients developing colorectal liver metastases (CRLM) over the course of their disease. The liver is the most frequent site of metastatic involvement, and the presence of CRLM is often associated with a poor prognosis. Effective management necessitates a comprehensive, multidisciplinary approach, involving collaboration between radiologists, oncologists, hepatobiliary and colorectal surgeons, and pathologists.

Advances in the management of CRLM have focused on maximizing tumor resection through surgical techniques such as R0 resection, two-stage hepatectomy, and ablative procedures, including radiofrequency and microwave ablation. These interventions offer the best prospects for long-term survival and potential cure. Additionally, for patients with initially unresectable disease, systemic therapies and targeted agents have shown the potential to convert inoperable disease into resectable states, significantly improving patient outcomes.

Given the complex nature of liver metastases in CRC, an integrated treatment strategy that combines surgical, ablative, and systemic therapies is essential. Further research into biomarker identification and novel therapeutic approaches will be crucial in optimizing treatment strategies for patients with CRLM. By prioritizing early detection, personalizing treatment plans, and ensuring ongoing surveillance, the quality of care can be enhanced, leading to improved survival

rates for patients confronting this difficult condition.

NOTES

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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